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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,200	FOURIE ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *7-21* is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/18/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Fig. 2 of paper by Abbaszade et al..

The Amendment of March 19, 2004 is acknowledged. The amendments to the claims have been entered. Claims 1-6 are cancelled. Claims 7, 9, 13, 14, 17, 18, 20 and are amended. Claims 7-21 are pending and are the subject of this Office Action.

DETAILED ACTION

1. Objections

1.1. Specification

The objection to the specification is withdrawn, because Applicants provided proof that the Accession No. for aggrecanase –1 and –2 quoted on page 8, lines 12 and 13, are valid.

2.2. Drawings

The objection to description to Fig. 2 is withdrawn in the light of Applicants' explanations.

3. Rejections

3.1. 35 USC, section 112, second paragraph

Rejection of claims 7-13 made in the Office Action of November 17, 2003 is withdrawn because the claims have been amended.

Rejection of claim 9 made in the Office Action of November 17, 2003 is withdrawn because the claim has been amended.

Rejection of claim 13 made in the Office Action of November 17, 2003 is withdrawn because the claim has been amended.

Rejection of claim 20 is withdrawn because the claim has been amended.

Claims 14-16 are rejected under 35 U.S.C. 112 as confusing. The claims were rejected, as being incomplete for omitting essential step. The amendment introduced as the omitted step the following: "wherein said measuring involves determining presence or absence of cleavage of said peptide." It is unclear whether Applicants intention is to detect only those compounds that completely inhibit the aggrecanase, i.e. no cleavage is observed, or to detect any compound that inhibits the activity, i.e., diminishes or prevents the cleavage. The rejection can be overcome by introducing the language suggested by the examiner in the last Office Action.

2.2. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.2.1. Lack of written description

Claim 7–21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 7-21 are rejected because neither the claims nor the specification teach that the inhibitor of the truncated form of aggrecanase inhibits also the wild type (full-length?) enzyme. The wild type enzyme is recited by preamble and the concluding step of the method, whereas the enzymatic reaction is performed by a truncated form of aggrecanase. Given the lack of evidence that disclosing an inhibitor of a truncated form is equivalent to disclosure of inhibitor of the full length enzyme Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Traversing this rejection Applicants write,

> "Applicants respectfully submit that the subject matter of claims 7-21 is clearly disclosed in the present specification. The present specification discloses that:
>
> > The Aggrecanases used in this invention can be full length, partial, truncated, chimeric or modified enzymes that still retain their ability to cleave the peptides as described in this invention. It has been demonstrated that Aggrecanse cleavage sites in aggrecan contain glutamic acid ion the N-terminal side

> of the cleavage site (P-1 position) and a non-polar or uncharged residue on the C-terminal side of the cleavage site (P1'position)…
>
> See page 8, lines 14-29. Thus, consistent with the understanding in the art, the truncated activities retain the expected activity" (page 7, line 17 of Remarks).

In this response Applicants do not address the question that an inhibitor of a truncated form of aggrecanase is also an inhibitor of any aggrecanase, particularly a wild type. Applicants do not disclose an inhibitor that inhibits both SEQ ID NO: 8, SEQ ID NO: 9 **and** any full-length aggrecanase. Thus, the argument is not persuasive.

However, Applicants response is related to the crucial question of what Applicants describe as the genus "aggrecanase" and what is the enzymatic activity of a protein called by Applicants "aggrecanase".

On page 1 and 2 of the specification Applicants define two species of the genus aggrecanase, i.e. ADAMTS-4 and ADAMTS-5 as Aggrecanase –1 having Genebank Accession NM 005099 and "Aggrecanase –2" having Genebank Accession NM 007038, wherein both enzymes cleave the site Glu373-Ala374 in the interglobular domain of aggrecan.

On page 2 under the subtitle "Summary of Invention" the term Aggrecanase –1 is defined as the polypeptide of SEQ ID NO: 8, consisting of amino acids 1-447, of which

amino acids 1-437 are identical to amino acids 1-437 of aggrecanse-1, ADAMTS-4 (NM 005099). In the same passage of the specification the term Aggrecanase-2 means the polypeptide of SEQ ID NO: 9 consisting of 1-492 amino acids of which amino acids 1-482 are identical to amino acids 1-482 of ADAMTS-5 (11) (NM 007038). According to teachings of Abbaszade I. et al., see the enclosed Fig.1, ADAMT-4 and –11 truncated to contain only 437 and 482 N-terminal amino acids do not contain disintegrin-like domains and trombospondin motifs that are crucial for degradation of aggrecan i.e. the ability to cleave the specific sites in aggrecan, i.e. Glu373-Ala374, Glu1545-Gly1546, Glu1714-Gly1715, Glu1019-Lys1920 and Glu1871-Lys1872 (Tortorella M. et al. J. Biol. Chem. 2000, 275, 18566-18573, included in IDS); see also Fig.1. Thus, structurally, both truncated forms disclosed by Applicants comprise metalloproteinase domains of aggrecanases, thus **they should be properly called metalloproteases derived from aggrecanase –1 and –2, because they are unable to cleave aggrecan.**

Using the term aggrecanase the scope of which covers full length, partial, truncated, chimeric or modified enzymes that still retain their ability to cleave the peptides as described in this invention is confusing, especially that according to the definition on page 7, line 28, the term aggrecanase includes also the capacity to cleave aggrecan and that capacity is not included in the definition of page 8, lines 14-29 quoted by Applicants in their traverse. Applicants do not disclose any enzyme that can cleave aggrecan and also can cleave any of the disclosed substrates. In addition, description of the genus of enzymes that still retain their ability to cleave the peptides as described in this invention is lacking written description, because, the sequences of the polypeptides

that are to be cleaved are not included. Not all peptides disclosed by Applicants are substrates for both SEQ ID NO:8 and 9, not to speak about any truncated aggrecanase.

Claim 7-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment introduces the limitation "wild type aggrecanase" which is not present in the specification or in claims as filed thus consistinga new matter.

Claims 7-9, 11-13 and 20-21 rejected in the Office Action of Nov 17, 2003 remain rejected. The claims are directed to a method of use of a large and variable genus of peptides that are less that 40 amino acids in length wherein the peptide comprises a cleavage site between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side polypeptides. Applicants disclose several representatives of the claimed genus identified by SEQ ID NOs: 3, 4, 5, 6 and 7. This is, however, insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Applicants fail to disclose any particular structure to function (of being cleavable by the truncated aggrecanase –1 and –2, i.e., SEQ ID NO: 8 and 9 or by any aggrecanase and its truncated form) relationship for a polypeptide that is less than 40 amino acids in

length, wherein the peptide comprises a cleavage site between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side of said polypeptide. No information, beyond the characterization of SEQ ID NO: 3, 4, 5, 6 and 7 has been provided by Applicants, which would indicate that they had possession of the claimed genus of these polypeptides. The data presented in Fig. 2 clearly prove that predictability of the function of the representatives of the claimed genus is not apparent. Some of the peptides are good substrates for metallopreotease derived from aggrecanse –1 and some are good substrates for metalloprotease derived from aggrecanase –2. The fact that a polypeptide of less than 40 amino acid long comprises a glutamic acid and as a neighbor on the C –terminal side of said glutamic acid a non-polar or uncharged amino acid is not sufficient for the polypeptide to be cleavable by SEQ ID NO: 8 or 9 or by full length ADAMTS-4 and ADAMTS-52. In addition, it is even less apparent which of such polypeptides are the substrates for any aggrecanase, i.e. any truncated form, mutated form, and aggrecanases from different animal species.

Given the lack of structural characteristics of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Traversing this rejection Applicants state,

"the present specification discloses (a) that the peptides 'included a collection of substrates for other proteases, as well as a number of sequences corresponding to membrane proximal cleavage sites of various proteins postulated to be released by metalloproteases' (see page 15, lines 16-20);(b) that two of the peptide sequences employed had particularly good activity (see page 16, lines 3-13); and (c) that additional peptides can serve as peptide substrates in accordance with the invention (see page 8-31). Thus, as disclosed in the specification 'those of ordinary skill in the art could similarly identify other [peptides] and test them in assays of this invention... "

The Applicants' arguments (a)-(c) are not persuasive for the following reasons. The fact that those skilled in the art, using the teaching of the Applicants are able to find other polypeptides that are substrates of SEQ ID NO: 8 and 9 is the question of enablement and not written description. Applicants themselves did not disclose all possible peptides that are less than 40 amino acids long and are the substrates of all full length, partial, truncated, chimeric or modified aggrecanases.

In addition, claims 7-8, 10-17 and 19-20, directed to a genus of methods of

using any truncated aggrecanase or any aggrecanase, rejected in the Office Action of Nov. 17, 2004 remain rejected. Applicants disclose two representatives of truncated forms of aggrecanase-1 and -2 set forth by amino acid sequence of SEQ ID NO: 8 and 9, which are metalloprotease parts of human aggrecanase-1 and 2 (ADAMTS-4 and ADAMTS-5). However, the claims are not limited to the truncated forms of aggrecanases consisting of metaloprotease domains, i.e.molecules in which disintegrin-like domain and trombospondin motifs are truncated. Thus, the description is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed large and variable genus of methods encompassing use of any aggrecanase or its truncated form any natural and man-made source. Not every truncated form of aggrecanase retains its activity, which, by definition is degrading of aggrecan. For example, a truncated form of aggrecanase-1 lacking the trombospondin motif 1 (TSP-1) is not effective in cleaving aggrecan; see Tortorella M. et al., J. Biol. Chem. 2000, August 18, 275/33, pages 25791-25797; enclosed to the Office Action and listed in the PTO Form 892.

Applicants fail to disclose any particular structure to function relationship identifying the genus of truncated polypeptides to be used in the claimed methods. Given the lack of structural characteristics of additional representative species of truncated aggrecanases as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Rejection of claim 21 for introducing new matter is withdrawn because the term "homologous" is deleted. However the claims is rejected under this paragraph as dependent on rejected claim 7.

2.2.2. Scope of invention

Claim 7-21 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for methods to detect compounds that inhibit aggrecanase-1 and –2 (metaloproteases of SEQ ID NO: 8 and 9) using peptides of SEQ ID NO: 3, 4, 5, 6 and 7 does not reasonably provide enablement for methods to detect compounds that inhibit any wild type aggrecanase (full length aggrecanase) using any peptide less than 40 amino acids in length comprising a cleavage site for any truncated aggrecanase wherein said site is located between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side polypeptides.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or

absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompass any method of identifying an inhibitor of any wild type aggrecanase using any peptide less than 40 amino acids in length and comprising a cleavage site for any truncated form of aggrecanase from any natural or man-made source, wherein said cleavage site is between a glutamic acid on the N-terminal side of the cleavage site and a non-polar or uncharged amino acid residues on the C-terminal side polypeptides.

Providing any truncated aggrecanase and wild type aggrecanase covered by the scope of the invention requires cloning extremely large number of genes originating from any animal or gene bank. The genes should be subsequently expressed in their full length or any truncated form and encoded polypeptide tested for aggrecanase acitivity using a standard substrate, i.e., the aggrecan fragment of more than 40 amino acids comprising as the cleavage site Glu-Ala mimicking residues Glu373-Ala374 of aggrecan molecule. After being successful in these lengthy and tedious procedures that are out of realm of the routine experimentation in the art, one skilled in the art has to design the polypeptides with the desired characteristics and test them for being a substrate for any of form of truncated aggrecanase.

While providing a peptide with claimed characteristics as a candidate substrate for aggrecanase truncated to metalloprotease, has certain probability of success, Applicants' own investigations indicate that this probability is low. Applicants' data presented in Figure 2 provide an evidence that in case of aggrecanase-1 the probability

is about 10% (6/56, taking those polypeptides for which the activity of cleaving is about 0.1 units) and in the case of aggrecanase-2 is even less, about 7% (4/56, taking into account those peptides for which the activity of cleaving is about 0.5 units). The probability of finding a peptide with the described characteristics that is a substrate for any truncated aggrecanase is even less, because Applicants' own data from Fig. 2 indicate that the probability of finding peptide that is a substrate for both SEQ ID NO: 8 and 9 is about 3/56, i.e., about 6%; see also page 5, line 31 of the specification where Applicants state, "One peptide [out of 56 tested, MW] was a good substrate for both truncated aggrecanase –1 and truncated aggrecanase –2." The one peptide out of 56 is less than 2%. More important, Applicants teach that the one out of 56 polypeptides is a substrate for metalloproteases derived from ADAMTS-4 and ADAMTS5/11 but the specification does not teach it is a substrate for any other truncated form of any aggrecanase or any full length aggrecanase.

Examiner concludes that without the further guidance on the part of Applicants regarding the structure of aggrecanases, their truncated forms and their substrates used in the claimed methods experimentation left to those in the art are improperly extensive and undue.

In response to this rejection Applicants argue, "Applicants respectfully submit that the present specification provides sufficient guidance to enable one of ordinary skill in the art to detect compounds that inhibit aggrecanase. The specification provides peptide sequences that have proven useful as substrates in an assay to detect aggrecanase

activity. The specification discloses that one of skill in the art can employ these peptides sequences to identify additional peptide sequences having the desired activity. The specification further discloses two truncated forms of aggrecanase that maintain the desired enzymatic activity and that these two forms can be employed in combination with the identified (and identifiable) peptides in an assay to identify inhibitors of aggrecanase."

Applicants' arguments have been fully considered but are found not persuasive for the following reasons.

Firstly, "peptide sequences that have proven useful as substrates in an assay to detect aggrecanase activity" are peptides that have proven useful only in detecting metalloprotease activity of ADAMT-4 or ADAMTS-5. Applicants failed to demonstrate that full-length ADAMT-4 or ADAMTt-5 are able to cleave any of the disclosed peptides. Neither Applicants have shown that other than SEQ ID NO: 8 and SEQ ID NO: 9 truncated forms of ADAMTS-4 and 5 can cleave said peptides. Neither any other wild type form or truncated form of any aggrecanase was show by Applicants to have this capacity.

As to the statement "The specification discloses that one of skill in the art can employ these peptides sequences to identify additional peptide sequences having the desired activity", it is unclear what activity Applicants mean. What desired activity?

Thirdly, Applicants have not demonstrated that the two truncated forms of aggrecanase i.e. SEQ ID NO: 8 and 9 maintain the enzymatic activity of aggrecanase,

i.e. cleaved aggrecan at specific sites. The prior art teaches that that would not be possible (Tortorella M. et al., J. Biol. Chem. 2000, August 18, 275/33, pages 25791-25797, quoted above and presented in examiners references.)

In summary, rejection of claims 7-21 under scope of enablement is not withdrawn.

2.3. Rejection under 35 USC section 103

Rejection of claims 7-9,11-13 and 20-21 under 35 U.S.C. 103(a) as being unpatentable over Tortorella et al. (The trombospondin motif of aggrecanase-1 (ADAMTS-4) is critical for aggrecan substrate recognition and cleavage, J. Biol. Chem. 2000, August 18, 275/33, pages 25791-25797) in view of the common knowledge in biotechnology is withdrawn, because Applicants arguments are found persuasive. Tortorella et al. disclose the cleavage site of the substrate, but not the substrate that is less tan 40 amino acid long.

3. Conclusion

All claims are rejected. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944 and the right fax number is (571) 273-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. EST.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner

ABBASZADE I. et al. JBC, 274(33), 23443-23450 (1999)

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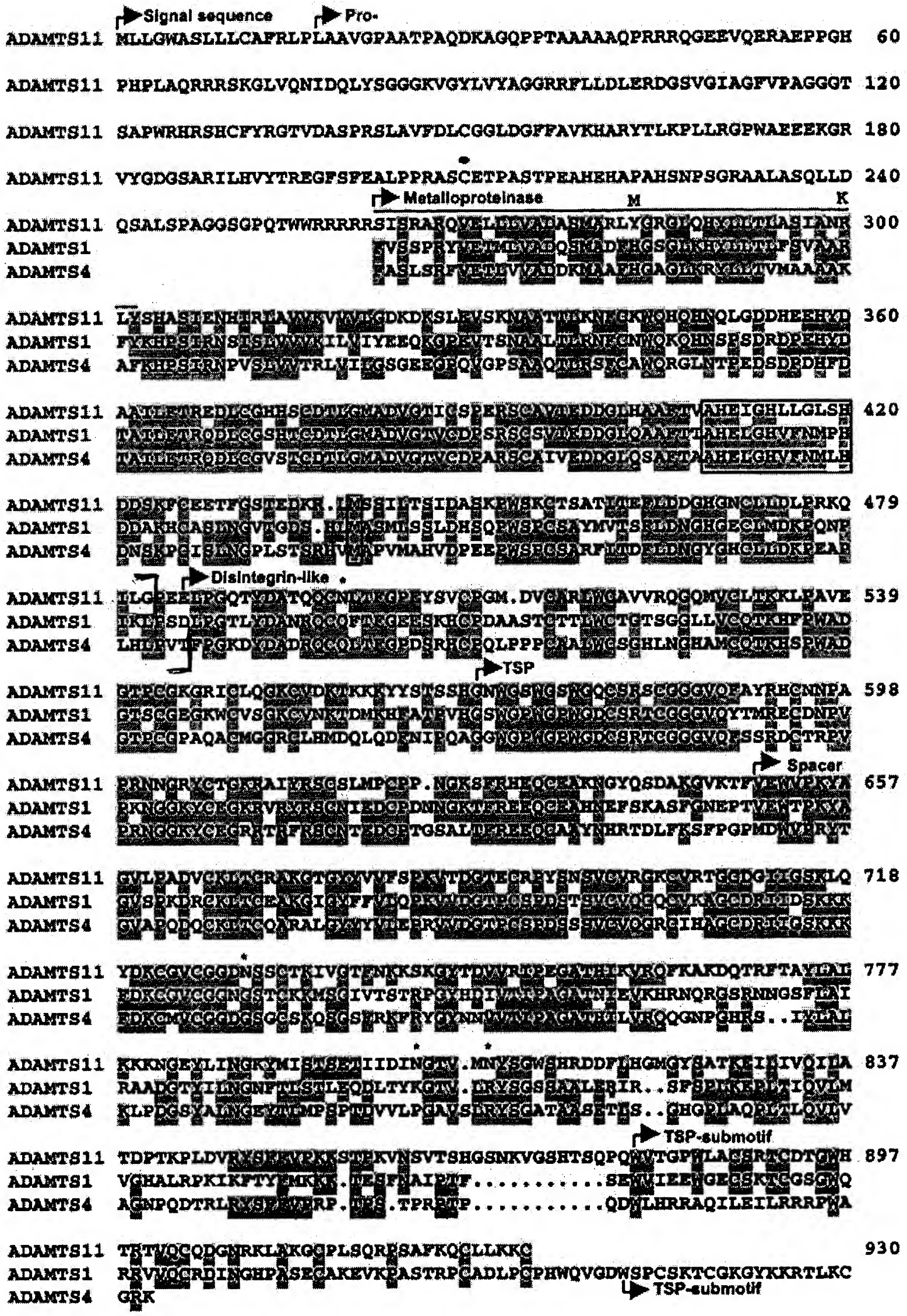

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